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Pesticides and Lung Cancer Risk in the Agricultural Health Study Cohort

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The authors examined the relation between 50 widely used agricultural pesticides and lung cancer incidence in the Agricultural Health Study, a prospective cohort study of 57,284 pesticide applicators and 32,333 spouses of farmer applicators with no prior history of lung cancer. Self-administered questionnaires were completed at enrollment (1993–1997). Cancer incidence was determined through population-based cancer registries from enrollment through December 31, 2001. A lung cancer standardized incidence ratio of 0.44 (95% confidence interval: 0.39, 0.49) was observed overall, due in large part to a low cigarette smoking prevalence. Two widely used herbicides, metolachlor and pendimethalin (for low-exposed groups to four higher exposure categories: odds ratio (OR) = 1.0, 1.6, 1.2, 5.0; $p_{trend} = 0.0002$; and OR = 1.0, 1.6, 2.1, 4.4; $p_{trend} = 0.003$, respectively), and two widely used insecticides, chlorpyrifos and diazinon (OR = 1.0, 1.1, 1.7, 1.9; $p_{trend} = 0.03$; and OR = 1.0, 1.6, 2.7, 3.7; $p_{trend} = 0.04$, respectively), showed some evidence of exposure response for lung cancer. These excesses could not be explained by previously identified lung cancer risk factors. The usage levels in this cohort are considerably higher than those typically experienced by the general population. An excess risk among spouses directly exposed to pesticides could not be evaluated at this time.

lung neoplasms; pesticides

Abbreviations: CI, confidence interval; OR, odds ratio.

Lung cancer is one of the most frequently diagnosed cancers in the world, and it is the leading cause of cancer death (1). Incidence and mortality trends for lung cancer closely parallel patterns of cigarette smoking, and it is estimated that cigarette smoking is associated with over 85 percent of all lung cancer in Western countries (1). As a group, farmers in most of these Western countries smoke less than the general population and, as a consequence, farmers usually experience a significantly reduced risk of lung cancer and other chronic diseases (2).

Lung cancer risk is causally associated with exposure to arsenical compounds (3), and an excess risk of lung cancer was observed among vineyard workers exposed to arsenic-based pesticides (4) and among arsenical pesticide manufacturers (5, 6). A variety of other pesticides have caused lung tumors in rodent bioassays, but the epidemiologic data supporting an association for nonarsenical pesticides and lung cancer risk in humans are mixed (7). In a study by Blair et al. (8) and a follow-up study by Pesatori et al. (9) of licensed pesticide applicators in Florida, the risk of lung cancer rose with the number of years licensed, with a standardized mortality ratio greater than 2.0 among those licensed for 20 years or more. In a survey of 1,600 agricultural applicators in East Germany, Barthel (9) observed almost a twofold excess mortality from lung cancer. The risk increased to 3.0 among those with 20 or more years of expo-

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sure (10). Although the specific agent(s) associated with the excess risk were not identified by Blair et al. or Barthel, Pesatori et al. observed lung cancer excesses with organophosphate and carbamate insecticides and phenoxyacetic acid herbicides (9).

A relation between exposure to phenoxy herbicides and/or contaminants (dioxins and furans) and lung cancer mortality was also observed in a cohort of workers from four manufacturing plants in Germany (11) and in a pooled analysis of 36 cohorts from 12 countries (12). Other studies of pesticide applicators (13, 14) and pesticide manufacturers (15–17), however, did not show any excess risk of lung cancer. The limited assessment of exposure, smaller sample size, and inadequate control of cigarette smoking in many of these studies underscore the need for improved investigations that focus on specific chemicals.

We examined the exposure-response relation between 50 important agricultural pesticides and lung cancer incidence in the Agricultural Health Study cohort while controlling for many known or suspected risk factors for lung cancer (1, 18–23).

MATERIALS AND METHODS

Cohort enrollment

The Agricultural Health Study is a prospective cohort study of 89,658 people, including 52,395 private applicators and 4,916 commercial applicators licensed to apply restricted-use pesticides and 32,347 spouses of private applicators from Iowa and North Carolina. Private applicators were farmers or nursery workers, and commercial applicators were persons employed by pest control companies or businesses that use pesticides. Pesticide applicators were enrolled when they completed an enrollment questionnaire. In Iowa, both commercial and farmer applicators attend the same pesticide certification testing sessions, and both were invited to participate in the study. In North Carolina, because private applicators attended separate training, only private applicators were enrolled. Private and commercial applicators were also asked to complete "take-home" questionnaires that sought more extensive information on occupational activities. Recruitment of applicators and their spouses began in December 1993 and continued until December 1997.

Questionnaires

The enrollment questionnaire sought information on the use of 50 pesticides (ever/never), crops grown and livestock raised, pesticide application methods used, personal protective equipment used, other agricultural activities and exposures, smoking, alcohol consumption, fruit and vegetable intake, medical conditions, medical conditions in first-degree relatives including a history of lung cancer, and basic demographic data (all questionnaires and publications resulting from this study are listed at http://www.aghealth.org). For 22 of the 50 pesticides in the applicator enrollment questionnaire, we also obtained information on the duration of use (years), frequency of use (days per year) and information on application methods, and use of protective equipment. For the remaining 28 pesticides listed in the enrollment questionnaire, exposure information was limited to ever versus never used. The take home questionnaire for applicators included detailed use information on the 28 pesticides reported as ever/never use in the enrollment questionnaire, more detailed information on personal protective equipment use, lifestyle characteristics, height and weight (used for body mass index), farm and nonfarm occupational exposure, multiple vitamin use, and hours spent in strenuous physical activity. The spouse questionnaire collected information only on ever/never use of the same 50 pesticides.

Cohort follow-up

Cohort members were matched to cancer registry files in Iowa and North Carolina for incident cancer identification and to the state death registries and to the National Death Index to ascertain vital status. One lung cancer case diagnosed after enrollment was excluded from the analyses because an earlier diagnosis of lung cancer was made prior to enrollment. Incident cancers were identified from enrollment (i.e., 1993–1997) through December 31, 2001. Study subjects alive but no longer residing in Iowa or North Carolina ($n = 875$) were identified through personal contacts with the study subject, motor vehicle records, pesticide registration records, and the current address records of the Internal Revenue Service, and they were censored in the year they left the state.

Analysis

A standardized incidence ratio for lung cancer (controlling for age, gender, and race) was computed relative to the populations of Iowa and North Carolina. Statistical significance of the standardized incidence ratios and 95 percent confidence intervals was based on standard methods (24, 25).

Since the follow-up period for case ascertainment was about 6 years and the lung cancer incidence rate did not vary appreciably, unconditional multivariate logistic regression (26) was used to compare lung cancer cases with noncases on a number of factors possibly associated with lung cancer risk. The odds ratio resulting from this procedure closely approximates the relative risk (26). In the analysis, we examined 50 pesticides using two different indices of exposure (i.e., lifetime exposure days and intensity-weighted lifetime exposure days) and other agricultural activities and exposures.

We replicated all analyses using two different reference groups to assess the risk associated with pesticide use. The first reference group included all applicators who did not mix or apply the specific pesticide. They were compared with exposed applicators grouped into three tertiles of pesticide use (lifetime days of use). The second reference group included applicators in the lowest tertile of specific pesticide use excluding never users, with the two tertiles of higher use as the exposed groups. In either analysis, if the upper tertile contained 10 or more exposed cases, it was further divided in two for the exposure response analysis. For the 22 pesticides

TABLE 1. Characteristics of licensed pesticide applicators and relations with the risk of lung cancer, Agricultural Health Study, 1993–2001

Characteristic	No. of lung cancer cases*	No. of cohort members (noncases)*	Adjusted odds ratio†	95% confidence interval	p_{trend}
Total	240	57,044			
Age (years)					
<55 (referent)	38	40,009	1.0		<0.001
55–59	41	5,598	5.7	3.3, 10.0	
60–64	57	4,848	9.8	5.8, 16.7	
65–69	50	3,482	11.3	6.4, 19.9	
70–74	35	1,985	17.2	9.3, 32.0	
≥75	19	1,120	14.9	6.7, 33.0	
Smoking status (pack-years)					
Never (referent)	13	29,237	1.0		<0.001
Former: <3.75	4	5,564	1.1	0.3, 4.0	
Former: 3.75–15	12	5,083	3.3	1.4, 7.5	
Former: >15	77	4,815	13.8	7.3, 26.1	
Current: <11.25	9	3,178	8.3	3.2, 21.6	<0.001
Current: 11.25–28.5	25	2,891	21.8	10.3, 46.0	
Current: >28.5	54	2,962	24.5	12.6, 47.8	
Sex					
Male	237	55,484	1.0		
Female	3	1,560	1.3	0.4, 4.1	
Race					
White	223	54,244	1.0		NA‡
Black/other	17	1,515	2.1	0.97, 4.2	
State of residence					
Iowa	82	36,698	1.0		NA
North Carolina	158	20,346	1.4	0.97, 2.0	
Education (years)					
<12 (referent)	75	5,290	1.0		0.09
12	104	25,995	0.8	0.5, 1.1	
>12	45	23,343	0.7	0.4, 1.1	

Table continues

included in the enrollment questionnaire, exposure information included 1) application-days/year; 2) total years of exposure; and 3) an exposure "intensity index" that includes information about the application method, whether the applicator repaired his/her own pesticide application equipment, and the use of protective equipment (27). Two exposure indices derived from these questionnaires and used in the analysis included 1) *lifetime exposure days* that were computed as follows: (application-days per year) × (total years of exposure) and 2) *intensity-weighted days* that were computed as follows: (application-days per year) × (total years of exposure) × (exposure intensity index). Similar detail for the remaining 28 pesticides was available only for the subset of applicators who returned the take-home questionnaire. Results for the 22 pesticides covered in detail on the enrollment questionnaire were compared for those who did and did not complete the take-home questionnaire. We could not assess risk among spouses who personally applied specific pesticides, because there were fewer than five lung cancer cases exposed to any single pesticide. We used a linear trend test to assess exposure response in applicators, treating the cumulative score as a continuous variable and also by treating the median of each exposure category as the quantitative score.

All odds ratios were adjusted for age as a categorical variable (<55, 55–59, 60–64, 65–69, 70–74, and ≥75 years), gender, smoking history by pack-years of exposure separately for current and former smokers (as a categorical variable), and total pesticide application days of any pesticide (continuous variable). We referred to this model as the "reduced model." To control more fully for potential confounders, we also included variables for nonfarm occupational exposures, regular recreational physical activity, alcohol consumption, fruit and vegetable intake, body mass index, medical conditions, medical conditions in first-degree relatives including a history of lung cancer, race, state of residence, license type, and education. This is referred to as the "comprehensive model." No meaningful differences

TABLE 1. Continued

Characteristic	No. of lung cancer cases*	No. of cohort members (noncases)*	Adjusted odds ratio†	95% confidence interval	p_{trend}
Pneumonia					
No (referent)	147	45,020	1.0		NA
Yes	59	8,758	1.5	1.0, 2.2	
Other chronic lung disease (bronchitis and emphysema)					
No (referent)	172	50,869	1.0		
Yes	37	2,582	2.0	1.2, 3.1	
Asthma					
No (referent)	193	50,676	1.0		
Yes	14	3,130	0.8	0.4, 1.5	
Family history of lung cancer					
No (referent)	180	48,830	1.0		NA
Yes	17	3,347	0.7	0.4, 1.3	
Vegetables (servings/week)					
≤4 (referent)	76	17,452	1.0		0.13
5–7	77	18,838	1.2	0.8, 1.8	
>7	53	15,769	0.8	0.5, 1.2	
Fruits (servings/week)					
≤2 (referent)	83	17,407	1.0		0.64
3–6	82	20,817	0.8	0.5, 1.2	
≥7	48	14,681	0.9	0.5, 1.4	
Alcohol intake (servings/time period)					
Never (referent)	103	17,352	1.0		0.45
≤3/month	41	17,186	0.7	0.5, 1.1	
≥1/week	69	18,858	1.0	0.7, 1.5	

* Missing data for some questions are responsible for differences in total cell counts.
† Odds ratios adjusted for all the other variables listed in the table.
‡ NA, not applicable.

were found between the exposure response when analyzed as a continuous or categorical variable, so only the categorical analysis results are presented. We computed odds ratios using both the reduced model and the comprehensive model. Since the odds ratios for lung cancer did not vary by more than 10 percent for any pesticide examined, we report results of the reduced model here. Trends in lung cancer risk also did not vary meaningfully when numbers of cigarettes smoked per day or duration of cigarette smoking in years was substituted for pack-years, so pack-years were used in all analyses. Institutional review boards approved the study proposal and the manner in which informed consent was obtained from study participants.

RESULTS

This analysis included both the 57,284 certified/licensed pesticide applicators and 32,333 spouses of private applicators with no history of lung cancer at enrollment. There were too few cases among commercial applicators to present analysis by individual license type at this time. A total of 2,209 deaths occurred among applicators during the mean follow-up period of 6.2 years, and 300 incident lung cancers were observed between enrollment and December 31, 2001. Based on state incidence rates, 622 lung cancer cases were expected, yielding a lung cancer standardized incidence ratio of 0.44 (95 percent confidence interval (CI): 0.39, 0.49).

Smoking cigarettes was a strong risk factor for lung cancer in the Agricultural Health Study cohort for both pesticide applicators (table 1) and spouses (table 2). Other significant lung cancer risk factors among pesticide applicators include age, a history of pneumonia, and other chronic respiratory diseases (i.e., bronchitis or emphysema) but not asthma. Elevated but nonsignificant excess lung cancer risks were observed among non-White compared with White applicators and among North Carolina applicators compared with Iowa applicators. Among spouses, age, emphysema, and chronic bronchitis were enumerated separately in their questionnaire, but no chronic lung disease, race, state of residence, or pneumonia was a significant risk factor for lung

TABLE 2. Characteristics of spouses of licensed private pesticide applicators and relations with the risk of lung cancer, Agricultural Health Study, 1993–2001

Characteristic	No. of lung cancer cases*	No. of cohort members (noncases)*	Adjusted odds ratio†	95% confidence interval	p_{trend}
Total	60	32,273			
Age (years)					
<55 (referent)	20	22,679	1.0		<0.001
55–59	9	3,667	0.92	0.3, 3.2	
60–64	10	2,904	1.8	0.6, 5.1	
65–69	11	1,774	6.0	2.4, 15.1	
70–74	7	861	7.0	2.1, 22.9	
≥75	3	384	5.1	0.6, 40.1	
Smoking status (pack-years)					
Never (referent)	21	21,974	1.0		
Former: <3.75	4	2,809	2.5	0.7, 8.6	<0.01
Former: 3.75–15	6	1,448	3.6	1.1, 13.5	
Former: >15	9	875	10.1	3.8, 27.1	
Current: <11.25	2	1,428	2.0	0.3, 15.8	<0.001
Current: 11.25–28.5	6	1,110	7.6	2.3, 24.4	
Current: >28.5	11	567	13.8	4.7, 40.4	
Sex					
Female	58	32,056	1.0		NA‡
Male	2	217	1.0		
Race					
White	60	30,776	1.0		NA
Black/other	0	546	NA		
State of residence					
Iowa	35	21,728	1.0		NA
North Carolina	25	10,545	0.5	0.2, 1.1	
Education (years)					
<12 (referent)	7	1,572	1.0		0.04
12	27	11,304	0.98	0.4, 2.7	
>12	16	15,209	0.4	0.1, 1.4	

Table continues

cancer among spouses. Among both applicators and spouses, we observed a reduced risk of lung cancer among those who completed some college compared with those that did not graduate from high school. A meaningful pattern of reduced lung cancer risk with vegetable or fruit consumption was not observed among pesticide applicators. Among spouses, a nonsignificant reduction in risk was observed for fruit consumption and vegetable consumption, and an unexpected decrease in lung cancer risk was observed among those who consumed at least four alcoholic beverages per month. Consumption of alcoholic beverages did not appreciably modify lung cancer risk among pesticide applicators.

Table 3 lists selected occupational exposures on and off the farm that were evaluated. Only off-the-farm exposures to asbestos (accounting for 16 exposed lung cancer cases) and lead (accounting for seven exposed lung cancer cases) were associated with an elevated lung cancer risk (asbestos: adjusted odds ratio (OR) = 2.2, 95 percent CI: 1.3, 3.7; lead: adjusted OR = 2.3, 95 percent CI: 1.1, 5.1) (data not shown). None of the farm-related activities was associated with lung cancer risk.

Table 4 displays odds ratios for applicators for the seven pesticides for which lifetime exposure days showed some evidence of an exposure-response relation. The following four pesticides exhibited significant tests of trend with increased lifetime days of use: metolachlor (chloracetanilide herbicide), chlorpyrifos (phosphorothioate insecticide), pendimethalin (dinitroaniline herbicide), and diazinon (phosphorothioate insecticide). The following three pesticides showed significant trends with increasing lifetime days of use when the "low-exposure group" was used as a reference but not when the "no-exposure group" was the reference: dicamba (a benzoic acid herbicide), carbofuran (a carbamate insecticide), and dieldrin (a chlorinated organic insecticide, no longer registered for use in the United States). Exposure-specific data for three of these seven chemicals (dieldrin, diazinon, and pendimethalin) were available only for those who completed the supplemental take-home questionnaire. No other significant exposure-response trends,

TABLE 2. Continued

Characteristic	No. of lung cancer cases*	No. of cohort members (noncases)*	Adjusted odds ratio†	95% confidence interval	p_{trend}
Pneumonia					
No (referent)	46	27,094	1.0		NA
Yes	11	3,612	0.8	0.3, 2.1	
Bronchitis					
No (referent)	50	29,410	1.0		NA
Yes	7	1,332	1.4	0.4, 5.1	
Asthma					
No (referent)	50	29,228			NA
Yes	7	1,507	1.7	0.5, 6.1	
Family history of lung cancer					
No	49	28,023			NA
Yes	9	2,664	1.3	0.5, 3.5	
Vegetable intake (servings/week)					
≤4 (referent)	11	4,022	1.0		0.09
5–7	23	8,198	0.93	0.4, 2.2	
>7	14	11,058	0.6	0.2, 1.7	
Fruit intake (servings/week)					
≤2	12	4,151	1.0		0.09
3–6	15	6,497	0.90	0.4, 3.1	
≥7	20	12,689	0.6	0.2, 1.6	
Alcohol intake (servings/time period)					
Never	36	14,030	1.0		0.05
≤3/month	18	13,167	0.5	0.2, 1.2	
≥4/month	5	3,732	0.2	0.04, 0.8	

* Missing data for some questions are responsible for differences in total cell counts.
† Odds ratios adjusted for all the other variables listed in the table.
‡ NA, not applicable.

either negative or positive, were observed among the other 43 pesticides evaluated in our analyses. For all 22 chemicals listed in the enrollment questionnaire, results were similar for those who did and did not complete the take-home questionnaire. There were insufficient numbers of spouses with lung cancer who had been exposed to individual pesticides to explore the risk related to direct exposure at this time.

Trends in lung cancer risk with exposure to any of these pesticides did not differ significantly by histologic type reported by either state cancer registry or by state of residence, but the number of exposed cases for any single histologic type or state of residence was small and these analyses will have to be repeated when additional cases are available. Trends in lung cancer risk with exposure to these pesticides were observed among both smokers and former smokers, but there were too few never-smoker cases to analyze.

For the four pesticides consistently associated with lung cancer risk among applicators in our analysis, intensity-weighted days of pesticide exposure generally produced lower estimates of lung cancer risk compared with lifetime exposure days. Metolachlor and pendimethalin (for highest vs. nonexposed groups: OR = 2.3, 95 percent CI: 0.9, 5.5, $p_{trend} = 0.67$; and OR = 4.4, 95 percent CI: 1.1, 17.6, $p_{trend} = 0.95$, respectively) and chlorpyrifos and diazinon (for highest vs. nonexposed groups: OR = 1.8, 95 percent CI: 1.0, 3.2, $p_{trend} = 0.04$; and OR = 1.4, 95 percent CI: 0.6, 3.8, $p_{trend} = 0.21$, respectively) showed an increase in lung cancer risk with increasing use of the pesticides, but the trend was significant only for chlorpyrifos.

DISCUSSION

Consistent with earlier reports (2), this report found that private applicators, who are mainly farmers, experienced a significantly lower risk of lung cancer compared with the general population, likely due to lower smoking rates. We also found that four heavily used agricultural pesticides, including two herbicides (i.e., metolachlor and pendimethalin) and two insecticides (i.e., chlorpyrifos and diazinon), were associated with a significant excess lung

TABLE 3. Farm tasks (days of exposure in lifetime) and off-the-farm jobs (ever vs. never) evaluated for an association with lung cancer, Agricultural Health Study, 1993–2001

Farm tasks	Off-the-farm job exposures
Till soil	Pesticides
Drive combine-harvester	Solvents
Plant	Gasoline
Natural fertilizer (manure)	Asbestos
Chemical fertilizer	X-rays
Hand-pick crops	Grain dust
Milk cows (summer)	Wood dust
Milk cows (winter)	Cotton dust
Drive truck (summer)	Mine dust
Drive truck (winter)	Engine exhaust
Drive diesel tractor (summer)	Solder
Drive diesel tractor (winter)	Welding fumes
Drive gas tractor (summer)	Electric-arc fumes
Drive gas tractor (winter)	Lead
Weld (summer)	Mercury
Weld (winter)	Cadmium
Repair engines (summer)	Other metals
Repair engines (winter)	Drilling tools
Grind metal (summer)	
Grind metal (winter)	
Grind animal feed (summer)	
Grind animal feed (winter)	
Clean with gasoline (summer)	
Clean with gasoline (winter)	

cancer risk in the Agricultural Health Study cohort. Three other pesticides including dicamba, a herbicide, and two insecticides, carbofuran and dieldrin, exhibited an increasing lung cancer risk with increasing lifetime days of use when the "low-exposure" group was used as the referent group but not when the "nonexposed" group was used as the referent group. These significant trends with lung cancer risk were observed after controlling for cigarette smoking, age, and other potential confounding risk factors. In addition, no meaningful differences in our results were found between the cohort members who completed the take-home questionnaire (i.e., 40 percent applicators) and those that did not, consistent with earlier observations made on this cohort (28). In a small nested case-control study of structural pesticide applicators in Florida, diazinon and the class of organophosphate and carbamate insecticide showed an approximate twofold excess lung cancer risk (9).

The four pesticides observed (i.e., metoachlor, pendimethalin, chlorpyrifos, and diazinon) have a significant exposure-response relation with lung cancer but did not have as strong an exposure response when intensity-weighted exposure days were used as an exposure metric. Since the current intensity index developed for the Agricultural Health Study gives particular weight to dermal exposure and not to potentially more relevant respiratory exposure (27), lung cancer risk estimates based on the intensity index may result in increased random error. Further insight into this exposure metric should be possible once field measures of pesticide exposure associated with work practices become available for the Agricultural Health Study cohort. Since we evaluated 50 pesticides and had no strong a priori hypotheses linking specific pesticides with human lung cancer risk, we cannot rule out the possibility that these are chance findings. We did not make adjustments for multiple comparisons because the appropriate methods are problematic when individual pesticides-specific analyses are not independent, as in our data.

A total of 44,193 cohort members (more than 77 percent of the cohort) were exposed to at least one of these seven pesticides (i.e., chlorpyrifos, diazinon, pendimethalin, metolachlor, dieldrin, dicamba, carbofuran), while a total of approximately 29.1 percent were exposed to three or more of these pesticides. These results suggest that a substantial portion of farmers and commercial pesticides applicators may be at an enhanced risk of lung cancer from working with pesticides currently registered for use in the United States and other countries.

Almost all the lung cancer cases that occurred in the Agricultural Health Study cohort were observed in current or former smokers. Although our findings remained after taking into account lifetime smoking using several different smoke exposure metrics, it is not possible to rule out residual confounding from cigarette smoking. It is also not yet possible to assess effect modification between pesticide exposure and cigarette smoking.

We observed a lower lung cancer risk in the lowest exposure days category for dicamba, metolachlor, pendimethalin, carbofuran, chlorpyrifos, and diazinon compared with those never exposed to these pesticides. Unidentified factors present in the nonexposed group but not in the exposed group might elevate risk among the nonexposed and be a source of confounding. In other contexts, authors have explained such an exposure-response curve as a result of hormesis (29), that is, the protective effect resulting from exposure to a subtoxic concentration of a chemical. While we are inclined to believe uncontrolled confounding is the most likely explanation for the shape of these exposure-response curves, additional epidemiologic and mechanistic data will be necessary before this question can be rigorously addressed.

Patterns of odds ratios with pesticide exposures were homogenous by histologic type of lung cancer. However, the power of the statistical tests was low. Effect modification with age or other occupational exposures was not observed. A family history of lung cancer among first-degree relatives conferred a small nonsignificant excess risk of lung cancer among spouses, which is consistent with some other reports (1, 30), but a family history effect was not observed among pesticide applicators.

Table 5 summarizes laboratory results for mutagenicity or carcinogenicity in animal bioassays of the seven chemicals associated with an elevated lung cancer risk in the Agricultural Health Study cohort (7). These data do not support our epidemiologic finding linking pesticide exposure to lung cancer risk. No evidence of animal carcinogenicity or

TABLE 4. Lung cancer risk among applicators by lifetime exposure days of indicated pesticide, using two referent groups, Agricultural Health Study, 1993–2001

Pesticide by lifetime exposure days	No. of exposed cases	Odds ratio*	95% confidence interval	Odds ratio*	95% confidence interval
Dicamba (herbicide; benzoic acid)					
No exposure	95	1.0	Referent		
<24.5	21	0.7	0.4, 1.1	1.0	Referent
24.5–108.5	19	0.9	0.5, 1.4	1.3	0.7, 2.5
108.6–224.7	8	1.1	0.5, 2.3	1.7	0.7, 4.0
>224.7	8	1.6	0.7, 3.4	3.1	1.2, 7.7
p_{trend}		0.15		0.04	
Metolachlor (herbicide; chloracetanilide)					
No exposure	96	1.0	Referent		
<38.8	20	0.6	0.4, 1.0	1.0	Referent
38.8–116	20	1.0	0.6, 1.6	1.6	0.8, 3.0
116.1–457.0	8	0.9	0.4, 1.8	1.2	0.5, 2.9
>457.0	6	4.1	1.6, 10.4	5.0	1.7, 14.9
p_{trend}		0.015		0.0002	
Pendimethalin (herbicide; dinitroaniline)					
No exposure	62	1.0	Referent		
<20.0	12	0.8	0.4, 1.4	1.0	Referent
24.5–56.0	10	1.3	0.6, 2.5	1.6	0.7, 3.9
56.1–224.7	6	1.6	0.6, 3.8	2.1	0.8, 6.0
>224.7	4	3.5	1.1, 10.5	4.4	1.2, 15.4
p_{trend}		0.005		0.003	
Carbofuran (insecticide; carbamate)					
No exposure	110	1.0	Referent		
<24.5	21	0.7	0.5, 1.3	1.0	Referent
24.5–108.5	11	1.1	0.6, 2.0	1.4	0.7, 3.1
>108.5	11	1.6	0.9, 3.2	2.3	1.0, 5.1
p_{trend}		0.08		0.05	
Chlorpyrifos (insecticide; phosphorothioate)					
No exposure	104	1.0	Referent		
<24.5	33	0.97	0.7, 1.4	1.0	Referent
24.5–103.0	13	1.0	0.6, 1.9	1.1	0.6, 2.1
103.1–116.0	12	1.7	0.9, 3.1	1.7	0.9, 3.4
>116.0	11	1.7	0.9, 3.3	1.9	0.9, 4.0
p_{trend}		0.02		0.03	
Diazinon (insecticide; phosphorothioate)					
No exposure	65	1.0	Referent		
<20.0	10	0.93	0.5, 1.8	1.0	Referent
20.0–108.5	11	1.4	0.7, 2.7	1.6	0.7, 3.9
>108.5	7	2.7	1.2, 6.1	3.2	1.1, 8.9
p_{trend}		0.008		0.04	
Dieldrin (insecticide; chlorinated organic)					
No exposure	80	1.0	Referent		
<8.7	5	1.4	0.6, 3.6	1.0	Referent
8.7–50.7	3	2.2	0.7, 7.3	1.9	0.4, 8.4
>50.7	3	5.3	1.5, 18.6	3.1	0.6, 16.0
p_{trend}		0.0.005		0.27	

* Odds ratios adjusted for smoking (pack-years among current and pack-years among former smokers), age, gender, and total days of any pesticide application.

TABLE 5. Summary of the toxicity, mutagenicity, and animal carcinogenicity of selected pesticides, Agricultural Health Study, 1993–2001

Pesticide	Use	Toxicity rating (EPA*,†)	Mutagenic?	Animal evidence for carcinogenicity	Carcinogenicity rating‡
Carbofuran	RUP*	I–II	Unlikely	No animal evidence	None
Chlorpyrifos	GUP*	II	No	No evidence for carcinogenicity from studies of rats and mice	None
Diazinon	RUP	II–III	Inconclusive	Improbable; no evidence for carcinogenicity from studies of rats	None
Dicamba	GUP	III	No	Improbable; no evidence for carcinogenicity from studies of rats	None
Dieldrin	Banned	Not listed	No	Shown to be hepatocarcinogenic in mice	EPA = class B2; IARC* = class 3
Metolachlor	GUP; some restricted	III	No	Unlikely; no evidence for carcinogenicity among male and female mice and among male rats; female rats given high doses for 2 years showed a significant increase in new growths, nodules, and lesions in livers at that dose	EPA = class C
Pendimethalin	GUP	III	No	No evidence of carcinogenicity from studies of mice	None

* EPA, Environmental Protection Agency; RUP, restricted-use pesticides; GUP, general-use pesticides; IARC, International Agency for Research on Cancer.
† EPA toxicity rating: I, highly toxic; II, moderately toxic; III, slightly toxic.
‡ EPA carcinogenicity rating: class B2, probable human carcinogen; class C, possible human carcinogen. IARC carcinogenicity rating: class 1, human carcinogen; class 2a, probable human carcinogen; class 2b, possible human carcinogen; class 3, not classifiable; class 4, probably not a human carcinogen.

mutagenicity is observed for six of the seven pesticides. A hepatocarcinogen in mice, dieldrin (which the US Environmental Protection Agency categorizes as a probable human carcinogen) is now banned from the US market. Metolachlor is associated with liver lesions in rats administered high doses and is listed by the US Environmental Protection Agency as a possible human carcinogen. Three insecticides, that is, carbofuran, chlorpyrifos, and diazinon, are considered highly toxic or moderately toxic, while the herbicides are generally considered only slightly toxic.

Other factors that contribute to lung cancer risk in the US population were shown to be significantly associated with lung cancer within the Agricultural Health Study cohort, including previous nonmalignant lung disease such as pneumonia and other chronic lung diseases (i.e., chronic bronchitis and emphysema), occupational exposure to asbestos and lead, and socioeconomic status (i.e., years of education). Dietary fruit and vegetable intake, alcohol consumption, and leisure-time physical activity were observed to be somewhat protective among spouses but not among the applicators in this analysis. None of these potentially confounding factors appeared to influence the observed associations between specific pesticides and lung cancer risk.

We found no association between lung cancer in spouses and direct use of any of the 50 pesticides. Currently, the number of lung cancer cases among the spouses is relatively small, limiting the interpretation of our data, and the analysis will be repeated when a larger number of spousal cases is available.

This study does have limitations. First, the exposure weights used in our algorithm are based on a literature review and not on direct measurements of exposure made within the study cohort. These weighting factors heavily emphasize dermal absorption over respiratory exposure, which may be generally appropriate but may be less appropriate for a study of lung cancer etiology. An exposure-monitoring effort within the study cohort is underway and will help to refine our estimates of exposure in the future. Second, some subjects in this study were asked to recall pesticide use from years ago. For the oldest members of the cohort, this was decades earlier. Although recall can be faulty after many years, previous evaluation of this issue has shown that recall of pesticide use by the Agricultural Health Study cohort is comparable with the recall of other variables such as diet and alcohol consumption, which have been used by epidemiologists in other studies as standard exposure measures (31). Third, follow-up of this cohort is relatively short, and it is not possible to evaluate time-dependent exposures and risk. Fourth, exposure-response analyses were performed on 50 pesticides, increasing the possibility that some or all of these findings could result from chance. Fifth, our analysis focused its attention on the active ingredients of formulated mixtures of commercial products used by private and commercial applicators. These formulations contain both active ingredients and so-called "inert ingredients," and we cannot rule out the possibility that the formulated mixture is responsible for the observed excess lung cancer risk.

The Agricultural Health Study has six principal strengths. First, the data collection prior to the diagnosis of cancer precludes the possibility of case-ascertainment bias. Second, detailed information on exposure for each pesticide, including years of use, applications per year, and applications in a lifetime, was used in the analysis. Third, ascertainment and statistical adjustment for age, smoking history, and other lung cancer risk factors mitigate the possibility of uncontrolled confounding. Fourth, the size of the study gives sufficient statistical power to examine the risk of exposure to a number of specific chemical exposures. Fifth, the outcome is cancer incidence obtained from population-based tumor registries, which eliminates issues related to survival when

mortality data are the outcome. Sixth, ongoing follow-up of the Agricultural Health Study cohort affords the opportunity to repeat the analyses on new incident lung cancer cases arising in the cohort.

In conclusion, at least four pesticides widely used currently in the United States and elsewhere have been found to be significantly associated with lung cancer risk. Inadequate control of the effect of smoking and less detailed pesticide exposure information may have masked these effects in earlier studies. Since we evaluated 50 pesticides with few a priori hypotheses linking these pesticides with human lung cancer risk, we cannot rule out the possibility that these are chance findings. Replication of these results in other studies and in continued follow-up in the Agricultural Health Study will be necessary before any firm conclusions can be reached.

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